UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,818	03/06/2002	Yoshihiro Ozeki	SAEG100.001APC	8140

20995 7590 03/17/2005

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
COLLINS, CYNTHIA E	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,818	OZEKI ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,8,11,12 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,8,11,12 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed December 20, 2004 has been entered.

Claims 1-4, 6-7, 9-10 and 13-20 are cancelled.

Claims 5, 8, 11, 12, 21, 22 and 25 are currently amended.

Claims 29 and 30 are newly added.

Claims 5, 8, 11-12 and 21-30 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

Claims 5, 8 and 11 remain rejected, and claims 22-30 are rejected, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the office action mailed July 14, 2004.

Applicant's arguments filed December 20, 2004 have been fully considered but they are not persuasive.

In response to the above ground of rejection, Applicants point out that claim 5 has been amended, and that claims 1, 3, and 4 have been cancelled. Applicants also point out that claims 8, 11, and 22-30 depend ultimately from claim 5, and Applicants maintain that claim 5 as

amended is believed to meet the written description requirement for the reasons that follow (reply pages 6-7).

In response to The Examiner's position that the disclosure of SEQ ID NO: 1 is not sufficient to enable other sequences within the genus, Applicants point out that the DNA of part (b), as amended, is a functional equivalent of the DNA of part (a) (SEQ ID NO: 1), and has a nucleotide which is at least 85% homologous to the nucleotide sequence of part (a) (SEQ ID NO: 1). Applicants also point out that The Examiner has indicated that claims directed to SEQ ID NO: 1 meet the requirements of 35 U.S.C. 112,first paragraph. Applicants respond that the skilled artisan would be able to isolate other genus members based upon the disclosed sequence corresponding to SEQ ID NO:1. (reply page 7)

In support of this position, Applicants have submitted Attachment 1 (Bureau T.E. et al. Tourist: a large family of small inverted repeat elements frequently associated with maize genes. Plant Cell. 1992 Oct;4(10):1283-94) and Attachment 2 (Bureau, T.E. et al. Stowaway: a new family of inverted repeat elements associated with the genes of both monocotyledonous and dicotyledonous plants. Plant Cell. 1994 Jun;6(6):907-16). Applicants maintain that these references disclose that MITES belonging to the same family have common nucleotide sequences in both terminal regions thereof. (reply page 7)

Applicants have also submitted Attachment 3 (Casacuberta E. et al. Presence of miniature inverted-repeat transposable elements (MITEs) in the genome of *Arabidopsis thaliana*: characterisation of the Emigrant family of elements. Plant J. 1998 Oct;16(1):79-85), which discloses a novel MITE, Emigrant, and cloning of 14 MITES belonging to the same family by in silico screening utilizing the characteristic of MITES that the sequence in both terminal regions

is highly conserved. Accordingly one skilled in the art at or before the time of the claimed invention could reasonably expect to be able to isolate functional equivalents of MITE-like elements such as SEQ ID NO:1 that had 85% sequence homology to SEQ ID NO:1 by hybridization, using the well known conservation of the 5' and 3' ends. (reply page 7)

Applicants have additionally submitted Attachments 4 (Biedler J. et al. Transposable element (TE) display and rapid detection of TE insertion polymorphism in the *Anopheles gambiae* species complex. Insect Mol Biol. 2003 Jun;12(3):211-6. Erratum in: Insect Mol Biol. 2003 Dec;12(6):659) and 5 (Casa A.M. et al. MITE display. Methods Mol Biol. 2004;260:175-88, 175 abstract), which attachments are directed to transposon display procedures which exploit the characteristic of MITES discussed above, that is, that the terminal regions are highly conserved. The technique is based upon the well known characteristic that MITES belonging to the same family have common nucleotide sequences in both terminal regions, which means that MITES belonging to the same family have common nucleotide sequences in both terminal regions to the extent that the sequence homology is at least 80% to allow hybridization. (reply page 7)

Applicants accordingly maintain that the claims as amended are believed to meet the written description requirement, as it was well known in the art that MITE sequences could be used to isolate other members of the genus having the recited property utilizing the property that the 5' and 3' ends are highly conserved. (reply page 8)

The Examiner maintains that the outstanding written description rejection was not predicated on the failure of the disclosure to enable other sequences within the genus. The outstanding written description rejection was predicated on the failure of the disclosure to

describe other sequences within the genus. Further, Applicants arguments directed to the ability of the skilled artisan to isolate other genus members based upon the disclosed sequence corresponding to SEQ ID NO:1 are not germane to the outstanding rejection, because whether a DNA sequence is described is not dependent on whether the specification provides an enabling disclosure. See *University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997), which discusses the description of a claimed human cDNA sequence based on the disclosure of a rat cDNA sequence and a method for obtaining the human cDNA sequence:

> The patent describes a method of obtaining this cDNA by means of a constructive example, Example 6. This example, however, provides only a general method for obtaining the human cDNA (it incorporates by reference the method used to obtain the rat cDNA) along with the amino acid sequences of human insulin A and B chains. Whether or not it provides an enabling disclosure, it does not provide a written description of the cDNA encoding human insulin, which is necessary to provide a written description of the subject matter of claim 5. The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. (*Lilly*, 43 USPQ2d at 1405)

In the instant case the disclosure of a single MITE DNA sequence of SEQ ID NO:1 and a general method for obtaining other MITE DNA sequences does not provide a written description of a DNA capable of causing duplication of the target sequence: (A)nG(A)n at the site of insertion thereof in a genomic gene, which DNA contains a plurality of repeat sequences represented by formula (1): XttgcaaY (wherein X represents g or t and Y represents a or c) in the terminal inverted repeat sequences thereof, and in the intermediate region between the terminal inverted repeat sequences, a plurality of repeat sequences represented by formula (1) and formula (2):

Zatgcma (wherein Z represents t or a), and which has a nucleotide sequence not less than 85% homologous with the nucleotide sequence shown under SEQ ID NO:1.

With respect to the Attachments 1-3, Bureau T.E. et al. (1992), Bureau, T.E. et al. (1994) and Casacuberta E. et al. do not support the description of the claimed invention because Bureau T.E. et al. (1992), Bureau, T.E. et al. (1994) and Casacuberta E. et al. do not describe MITE-like elements that have the structural and physical features of the claimed MITE-like elements.

With respect to the Attachments 4-5, Biedler J. et al. and Casa A.M. et al. cannot support the description of the claimed invention, because the claimed invention must be described at the time of filing, and Biedler J. et al. (2003) and Casa A.M. et al. (2004) were published after the earliest effective filing date for the instant application (July 21, 1999).

Applicants also maintain that amendment of the claims such that they no longer recite "perfect" or "imperfect" terminal repeat sequences is believed to address the issue raised with respect to the specification not describing MITE-like elements that are capable of causing duplication of a genus of target sequences (A)nG(A)n (n being an integer not less than 1) at the insertion site thereof in a genomic gene and that have a genus "perfect terminal inverted repeat sequences in their 5' and 3' terminal regions or that have a genus of imperfect terminal inverted repeat sequences in their 5' and 3' terminal regions. Applicants point out, however, that the characteristic that the isolated MITE "is capable of causing duplication of the target sequence: (A)nG(A)n" is merely a characteristic of the claimed DNA, and Applicants maintain that it is not necessary to explain the mechanism behind transposition of MITE-like sequences in order to isolate other MITE-like sequences and in order to use the invention as claimed, as other MITE-

like sequences may be isolated by utilizing the well-known conservation of sequence at the 5' and 3'ends. Applicants also point out that The MITE-like sequences have a disclosed use as transcription activation elements as shown in Figures 12 and 13, where the inclusion of the IS1 and/or IS2 element when transforming tobacco cells leads to more viable cells due to an increase in expression of kanamycin resistance in the cells (reply page 8).

The Examiner maintains that Applicants have not describe a MITE-like element that is capable of causing duplication of the target sequence: (A)nG(A)n. Further, the outstanding rejection imposed no requirement that the mechanism behind transposition of MITE-like sequences be explained. Additionally, as discussed above, Applicants arguments directed to the ability of the skilled artisan to isolate other genus members are not germane to the outstanding rejection, because whether a DNA sequence is described is not dependent on whether the specification provides an enabling disclosure. Further, the Examiner maintains that Figures 12 and 13 do not describe the IS1 and/or IS2 elements as increasing expression of kanamycin resistance in the cells. Figure 12 describes the results of Example 3 "in which a comparison was made among the numbers of regenerated calli on selection media containing kanamycin, from cultured tobacco BY-2 cells transformed by introduction of the pIS2-35S/AB35S constructs (IS2) pISl-35S/AB35S (IS1), pIS12-35S/AB35S (IS12) and pAB35S (35S) (control)." (specification pages 17-18). Figure 12 describes the results of Example 3 "in which a comparison was made between the GUS activity of tobacco calli (control) resulting from introduction of pAB35S (35S) (left graph) and the GUS activity of tobacco calli resulting from Introduction of pIS12-35S/AB35S (IS12) (right graph)." (specification page 18).

Applicants additionally maintain that amendment of claim 5 to recite "not less than 85% homologous with the nucleotide sequences shown under SEQ ID NO:1" is believed to address the issue raised with respect to the specification not describing a DNA having a complementary sequence to SEQ ID NO: 1 under stringent conditions. (reply page 9)

Amendment of claim 5 to recite "not less than 85% homologous with the nucleotide sequences shown under SEQ ID NO:1" does not address the issue raised with respect to the specification not describing a DNA having a complementary sequence to SEQ ID NO: 1 under stringent conditions. Regardless of how the claims articulate the relationship of the claimed sequences to SEQ ID NO:1 (ability to hybridize to SEQ ID NO:1 versus percent homology with SEQ ID NO:1), the specification does not describe a genus of sequences related to SEQ ID NO:1, as the specification describes only the single sequence of SEQ ID NO:1.

In response to the assertion in the office action that the specification does not describe or characterize any element or construct containing at least one MITE-like element that has transcriptional activation activity, Applicants point out that the specification describes 3 different MITE/promoter fusion constructs, and that The activity of these constructs is described in Figures 12 and 13. Applicants point to Figures 12 and 13 as showing that the inclusion of the IS 1 and/or IS2 element when transforming tobacco cells leads to more viable cells due to an increase in expression of kanamycin resistance in the cells which include the IS 1 and/or IS2 element. Consequently, Applicants believe that there is sufficient written description for "transcriptional activation activity" in the present specification based upon the characterization of these three different constructs. (reply page 9)

As discussed above, the Examiner maintains that Figures 12 and 13 do not describe the IS1 and/or IS2 elements as "increasing expression" of kanamycin resistance in the cells. The Examiner also maintains that Figures 12 and 13 do not describe the IS1 and/or IS2 elements as having "transcriptional activation activity".

In response to the assertion in the office action that the specification does not describe or characterize any transcriptional activation element containing at least one MITE-like element that functions as a transposable element, Applicants submit that one skilled in the art would identify the described MITE-like elements as transposable elements based upon their characteristics as claimed and as described in the present specification. (reply page 9)

The Examiner maintains that one skilled in the art would not identify the described MITE-like elements as transposable elements based upon their characteristics as claimed and as described in the present specification. Neither Applicant nor the prior art have established that any MITE can transpose. In this regard Applicants' own specification discloses at page 3 lines 5-8 that "for MITEs, no reports have so far been made about evidence of their transposition in the genome in spite of their being very similar to DNA type ones". Applicants' specification also discloses at page 4 lines 13-15 that "As far as plant-derived MITEs are concerned, however, no such transposase-encoding open reading frame has been discovered".

In response to the assertion in the office action that the specification does not describe a genus of recombinant DNA constructs comprising a tandem coupling product from a MITE-like element, Applicants point out that such a tandem coupling product is described, for example, at

page 30, lines 12-23 and is also exemplified at page 48, line19 to page 49, line 6 and also Figure 9. (reply page 9)

As set forth at page 7 lines 1-4 of the previous office action, the Examiner maintains that the disclosure of a single DNA construct of SEQ ID NO:3 in which IS2 (SEQ ID NO:1) and IS1 (SEQ ID NO:2) are cloned in tandem does not describe the claimed genus of recombinant DNA constructs comprising a tandem coupling product from a MITE-like element.

Applicants maintain that they were the first to discover this particular family MITE-like elements, and that limitation of the claims to this single embodiment would unfairly allow others to easily practice Applicants' invention without infringing Applicants claim by using the methodology as discussed above and as disclosed in the five (5) attached references to isolate other MITE-like elements within the genus. As Applicants were the first to discover this family of MITE-like elements, Applicants believe that they are entitled at least to the claim breadth a recited in claim 5 as amended (reply pages 9-10).

Applicants' arguments are not germane to the outstanding rejection because they are not directed to showing that the statutory requirements for written description have been met. As set forth at page 7 of the previous office action, the description of a genus of DNA sequences may be achieved by means of recitation of a representative number of DNA sequences defined by nucleotide sequence, falling within the scope of the genus, or by means of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. In the instant case Applicant has neither recited a representative number of

DNA sequences, or otherwise established the structural features common to members of the genus.

Claims 5, 8, 11-12 and 21 remain rejected, and claims 21-30 are rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated miniature inverted-repeat transposable element (MITE)-like element having the nucleotide sequence of SEQ ID NO:1, a recombinant DNA element having the nucleotide sequence of SEQ ID NO:3, and a recombinant DNA element having the nucleotide sequence of SEQ ID NO:14, does not reasonably provide enablement for other isolated MITE-like elements, or isolated MITE-like elements that are capable of causing duplication of a target sequence, or other recombinant DNA elements, or recombinant DNA elements that activate transcription or that transpose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record set forth in the office action mailed July 14, 2004.

Applicant's arguments filed December 20, 2004 have been fully considered but they are not persuasive.

Applicants maintain that this rejection is similar to the rejection above and Applicants' comments above are incorporated herein by reference. (reply page 10)

The Examiner disagrees with Applicants' assessment that outstanding enablement rejection is similar to the outstanding written description rejection, as the written description requirement is separate and distinct from the enablement requirement. In re Barker, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v.

Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) See MPEP 2161. In the instant case the rejections differ in that the outstanding written description rejection was predicated on the failure of the specification to adequately describe the structural and physical features of the claimed genus of MITE-like sequences, whereas the outstanding enablement rejection was predicated on the failure of the specification to provide sufficient guidance for making and using the claimed genus of MITE-like sequences.

In response to the Examiner's position that it would require undue experimentation to obtain genus members other than SEQ ID NO: 1 and that it is not predictable that other MITE-like elements that structurally and functionally resemble the IS2 mite of SEQ ID NO: 1 could be found in other plant species, Applicants argue that isolation of related MITE-like elements was well known at the time of the invention, and that this position is supported by the 5 references provided. In addition, Applicants have limited the claims to either SEQ ID NO: 1 (which the Examiner admits is enabled) or to "a DNA capable of causing duplication of the target sequence:(A)nG(A)n at the site of insertion thereof in a genomic gene, which contains a plurality of repeat sequences represented by formula (1): XttgcaaY(wherein X represents g or t and Y represents a or c) in the terminal inverted repeat sequences thereof, and in the intermediate region between the terminal inverted repeat sequences, a plurality of repeat sequences represented by formula (1) and formula (2): Zatgcu (wherein Z represents t or a)" which is also 85% homologous to SEQ ID NO: 1. Applicants maintain that the scope of the claim is clearly defined and that it was within the skill in the art to isolate such sequences. Applicants further maintain that one skilled in the art would expect to find other sequences falling within the scope

of the present claims, as indicated by the attached references. Consequently, Applicants submit that the present claims are of appropriate scope and are enabled by the present specification. (reply pages 10-11)

The Examiner maintains that while the isolation of unrelated MITE-like elements was well known at the time of the invention, the isolation of the MITE-like elements related to those claimed was not. In this regard Applicants own specification discloses at page 19 lines 19-22 that the IS2 element (SEQ ID NO:1) "can be said to be an insertion element belonging to a novel family different from any of the so far known families."

Further, the 5 references provided do not support the enablement of Applicants' invention because none disclose the isolation of MITE-like elements related to those claimed using the techniques disclosed in the specification.

Bureau T.E. et al. (1992) disclose the isolation of a 128 bp MITE sequence (Tourist-Zm-1) that has a 14 bp terminal inverted repeat sequence, a subterminal pentamer repeat, and is associated with the target sequence TAA, whereas Applicants disclose the isolation of a 769 bp MITE of SEQ ID NO:1 (IS2) that has 158 bp imperfect inverted terminal repeat sequences and is associated with the target sequence AAAAGAAAA. Further, the Tourist-Zm-1MITE disclosed by Bureau T.E. et al. (1992) was isolated by using maize waxy gene primers for PCR amplification of an insertion in the maize waxy gene, whereas Applicants isolated SEQ ID NO:1 by hybridizing a carrot phenylalanine ammonia-lyase (PAL) cDNA to a carrot genomic DNA library to obtain a carrot PAL genomic DNA (gDCPAL3).

Bureau, T.E. et al. (1994) disclose an isolated 255 bp MITE sequence (Stowaway-Sb1) that has an 11 bp terminal inverted repeat sequence and is associated with the target sequence

TA, whereas Applicants disclose the isolation of a 769 bp MITE of SEQ ID NO:1 (IS2) that has 158 bp imperfect inverted terminal repeat sequences and is associated with the target sequence AAAAGAAAA. Further, the Stowaway-Sb1 MITE disclosed by Bureau T.E. et al. (1994) was isolated by hybridizing a sorghum phosphoenolpyruvate carboxylase CP21 cDNA to a sorghum genomic DNA library to obtain a sorghum phosphoenolpyruvate carboxylase CP21 gene, whereas Applicants isolated SEQ ID NO:1 by hybridizing a carrot phenylalanine ammonia-lyase (PAL) cDNA to a carrot genomic DNA library to obtain a carrot PAL genomic DNA (gDCPAL3).

Casacuberta E. et al. disclose the identification of 14 members of a class of MITE sequences designated Emigrant that range in size from 235 bp to 604 bp, that have 24 bp terminal inverted repeats, and that are associated with the target sequence TA, whereas Applicants disclose the isolation of a 769 bp MITE of SEQ ID NO:1 (IS2) that has 158 bp imperfect inverted terminal repeat sequences and is associated with the target sequence AAAAGAAAA. Further, the first Emigrant family MITE sequence disclosed by Casacuberta E. et al. was isolated by genomic sequencing of chromosome IV of *Arabidopsis thaliana*, whereas Applicants isolated SEQ ID NO:1 by hybridizing a carrot phenylalanine ammonia-lyase (PAL) cDNA to a carrot genomic DNA library to obtain a carrot PAL genomic DNA (gDCPAL3).

Biedler J. et al. disclose the use of a technique called transposable element (TE) display which employs adaptor ligation and primer-specific amplification to identify genomic insertion sites of Pegasus, TAA-II-Ag, TA-III-Ag and TA-Iα-Ag MITEs in the *Anopheles gambiae* genome. Applicants' disclosure make no reference to a technique like transposable element (TE)

display, and the Pegasus, TAA-II-Ag, TA-III-Ag and TA-Iα-Ag MITEs do not appear to be related to the claimed MITE-like sequences.

Casa A.M. et al. disclose the use of a technique called MITE display which employs adaptor ligation and primer-specific amplification to identify genomic insertion sites of Heartbreaker (Hbr) MITEs in the maize genome. Applicants' disclosure make no reference to a technique like MITE display, and Heartbreaker (Hbr) MITEs do not appear to be related to the claimed MITE-like sequences.

As set forth at pages 13-14 of the prior office action, the full scope of the claimed invention is not enabled because the specification does not provide sufficient guidance with respect to where and how to obtain other MITE-like elements that structurally and functionally resemble the IS2 MITE of SEQ ID NO:1. Such guidance is necessary because one cannot predictably obtain MITE-like elements that structurally and functionally resemble the IS2 MITE of SEQ ID NO:1 from other sources. The specification itself discloses at page 45 that the IS2 MITE of SEQ ID NO:1 has no homology with known transposable elements, such that it constitutes a novel family belonging to none of the so far known transposable element families. Furthermore, the prior art also teaches that other plant MITE-like elements may be detected in some plant species but not others. See, for example, Bureau T.E. et al. (A computer-based systematic survey reveals the predominance of small inverted-repeat elements in wild-type rice genes. Proc Natl Acad Sci U S A. 1996 Aug 6;93(16):8524-9), who teach that nine putative mobile element families, including the MITE-like elements Tourist and Stowaway, are detected in the genome of rice, but not *Arabidopsis* (page 8524 abstract and page 8527 column 1 last paragraph). Given the unpredictability of identifying other MITE-like elements that structurally

and functionally resemble the IS2 MITE of SEQ ID NO:1 in other plant species, it would require undue experimentation for one skilled in the art to identify and clone from undisclosed sources such elements, as one skilled in the art would have to first identify by trial and error those plant species that potentially harbor such elements, and then isolate and characterize candidate element to confirm its identity.

In response to the Examiner's assertion that the specification does not provide sufficient guidance with respect to how to use the disclosed MITE-like sequences to duplicate a target sequence or transpose, Applicants maintain that the characteristic that the isolated MITE is "capable of causing duplication of the target sequence: (A)nG(A)n" is merely a characteristic of the claimed DNA. That is, other MITE-like sequences falling within the genus also have a target duplication sequence as claimed. Applicants maintain that it is not necessary to explain the mechanism behind transposition of MITE-like sequences in order to isolate other MITE-like sequences and in order to use the invention as claimed. As explained above, other MITE-like sequences may be isolated by utilizing the well-known conservation of sequence at the 5' and 3' ends. (reply page 11)

The Examiner maintains that Applicants have not disclosed a MITE-like element that is capable of causing duplication of the target sequence or transposition, or how to use a MITE-like element of SEQ ID NO:1 to cause duplication of the target sequence or to transpose. Also, the Examiner maintains that the rejected claims do not require that the MITE-like elements "have a target duplication sequence"; the rejected claims require that the MITE-like elements be "capable

of causing duplication of a target sequence". Additionally, the outstanding rejection imposed no requirement that the mechanism behind transposition of MITE-like sequences be explained.

Further, Applicants arguments that other MITE-like sequences may be isolated by utilizing the well-known conservation of sequence at the 5' and 3' ends are not germane to the issues of using the other MITE-like sequences to cause duplication of a target sequence or to transpose, as neither Applicants nor the prior art disclose how to use MITEs to cause duplication of a target sequence or to transpose. In this regard Applicants' own specification discloses at page 3 lines 5-8 that "for MITEs, no reports have so far been made about evidence of their transposition in the genome in spite of their being very similar to DNA type ones". Applicants' specification also discloses at page 4 lines 13-15 that "As far as plant-derived MITEs are concerned, however, no such transposase-encoding open reading frame has been discovered".

In this regard Applicants' attention is also redirected to pages 14-15 of the previous office action which sets forth the teachings of Wessler S. R. et al. (LTR-retrotransposons and MITEs: important players in the evolution of plant genomes. Curr Opin Genet Dev. 1995 Dec;5(6):814-21. Review), who teach that while MITES have structural elements in common with known transposable elements, MITES have no coding potential, and it is not known by what mechanism (DNA or RNA) a MITE may transpose (page 818 column 1 third paragraph and column 2 last paragraph). Wessler S. R. et al. further teach that if MITES are DNA elements their mobilization would require transposase activity encoded by another element or genetic locus, and that no MITE has been shown to excise, which may indicate low transposase activity or that MITES present in the genome are no longer transpositionally active (page 819 column 1 first paragraph). Given the uncertainty of whether and how MITE-like sequences could cause duplication of a

target sequence or transpose, it would require undue experimentation for one skilled in the art to determine how to induce a MITE to exhibit such activity, as one skilled in the art would have to identify by trial and error both a MITE transposition event and the other element or genetic locus that was the cause of the event.

Applicants also maintain that The MITE-like sequences have a disclosed use in the specification as transcription activation elements. Applicants point in particular to Figures 12 and 13, which show that inclusion of the IS1 and/or IS2 element when transforming tobacco cells leads to more viable cells due to an increase in expression of kanamycin resistance in the cells which include the ISI and/or IS2 element. In response to the Examiner's concerns as to whether the specification teaches how to activate transcription, Applicants maintain that they have shown increased growth due to increased expression of kanamycin resistance in three different species; tobacco, carrot and rice; in whole plants (tobacco) and undifferentiated cells (tobacco and rice) and somatic embryos (carrot); in dicots (tobacco and carrot) and monocots (rice), and that the results were consistent for these diverse species and tissue types. Applicants also maintain that while the Examiner states that other mechanisms could be proposed to account for the increased transformation efficiency and regeneration efficiency, it is not necessary for Applicants to understand the mechanism by which their invention works. Applicants maintain that the results are clear and consistent that MITE-like elements according to the invention produce an increase in growth, and that Consequently one skilled in the art would recognize that the claimed elements could be used to activate transcription. (reply page 11)

The Examiner maintains that the claimed sequences are not disclosed as being capable of activating transcription, and that the specification does not provide sufficient guidance with respect to how to use the claimed sequences to activate transcription. In this regard the Examiner still maintains that Figures 12 and 13 do not describe the IS1 and/or IS2 elements as "increasing expression" of kanamycin resistance in the cells. Figure 12 describes the results of Example 3 "in which a comparison was made among the numbers of regenerated calli on selection media containing kanamycin, from cultured tobacco BY-2 cells transformed by introduction of the pIS2-35S/AB35S constructs (IS2) pISl-35S/AB35S (IS1), pIS12-35S/AB35S (IS12) and pAB35S (35S) (control)." (specification pages 17-18). Figure 12 describes the results of Example 3 "in which a comparison was made between the GUS activity of tobacco calli (control) resulting from introduction of pAB35S (35S) (left graph) and the GUS activity of tobacco calli resulting from Introduction of pIS12-35S/AB35S (IS12) (right graph)." (specification page 18).

The Examiner additionally maintains that Applicants have not shown increased growth due to increased expression of kanamycin resistance. As set forth at pages 12-13 of the previous office action, the Examiner maintains that the specification teaches only that an increased yield of transformant calli was observed when cultured BY-2 tobacco cells were transformed with pIS2-35S/AB35S or pIS12-35S/AB35S (pages 57 Table 1; page-58), that increased GUS activity was observed when cultured BY-2 tobacco cells were transformed with pIS12-35S/AB35S (Figure 13; pages 59-60), that an increase in shoot regeneration efficiency was observed when SR1 tobacco leaf discs were transformed with pIS2-35S/AB35S or pIS12-35S/AB35S, (page 62 Table 2; pages 62-63), that improved regeneration efficiency in the presence or absence of 2,4-D

was observed when carrot somatic embryos were transformed with pIS2-35S/AB35S, pIS12-35S/AB35S and pMU3-35S/AB35S (page 65 Table 3; pages 63-66), and that improved regeneration efficiency was observed when rice seeds were transformed with pIS2-35S/AB35S (page 69 Table 4; pages 66-69). One skilled in the art would not recognize that the claimed elements could be used to activate transcription on this basis because, as set forth at pages 15-16 of the prior office action, it is unpredictable whether the disclosed MITE-like sequences and recombinant DNA elements comprising these sequences actually function to activate transcription, since a variety of other different mechanisms other than transcriptional activation could be proposed to account for the increased transformation efficiency and improved regeneration efficiency observed in plant cells transformed with expression vectors comprising the disclosed MITE-like sequences and genetic constructs.

The Examiner further maintains that the outstanding rejection imposed no requirement that Applicants to understand the mechanism by which transcriptional activation occurs. While it was asserted at pages 15-16 of the previous office action that the specification does not provide sufficient guidance with respect to how to use the disclosed MITE-like sequences to activate transcription, and that such guidance is necessary because it is unpredictable whether the disclosed MITE-like sequences and recombinant DNA elements comprising these sequences actually function to activate transcription, such guidance need not be provided in the form of explaining the mechanism by which MITE-like sequences activate transcription. Such guidance could, for example, be provided by disclosing that the activation of transcription occurs when a construct comprising a MITE-like sequence of SEQ ID NO:1 is transformed into a plant cell. In the instant case, while Applicants have provided guidance with respect to how to use the

disclosed MITE-like sequences to increase transformation efficiency and improve regeneration efficiency in plant cells, Applicants have not provided guidance with respect to how to use the disclosed MITE-like sequences to activate transcription.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Remarks

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins
Examiner
Art Unit 1638

CC

Cynthia Collins 3/15/04